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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
VOGEL, NANCY T	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 10/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/076,117	BERMUDES ET AL.	
	Examiner	Art Unit	
	Nancy Vogel	1636	

-- Th MAILING DATE of this communication appears on the cover she t with the correspondence addr ss --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-24 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-24 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 13 February 2002 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-24 are pending in the case.

Specification

The disclosure is objected to because of the following informalities: page numbers on the Table of Contents pages of the specification (i-ii) do not correspond to the numbering of the rest of the specification.

Appropriate correction is required.

Claim Objections

Claims 19, 20 and 24 are objected to because of the following informalities: "in which the solid tumors is" is improper grammar. "Phagmid" is misspelled. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in formulating this rejection (In re Wands, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the

nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction of guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The present claims are very broad. Claim 1 covers a pharmaceutical composition comprising an attenuated, tumor-targeting Gram-negative bacterium containing a bacteriophage wherein the bacteriophage encodes a gene product of interest either under the control of an eukaryotic promoter or as part of a fusion with a capsid protein. Claim 8 covers a kit comprising the pharmaceutical composition of claims 1. Claim 9 covers a kit comprising the pharmaceutical composition of claim 1 wherein the bacterium is expressing the F' pilus. Claim 11 covers a method for delivering an agent comprising administering the composition of claim 1. Claim 14 covers a method for delivering an agent comprising the administering the composition of claim 1 wherein the bacterium is expressing the F'pilus. Claim 15 covers a method of inhibiting tumor growth or reducing tumor volume comprising administering a tumor-targeting bacterium containing a bacteriophage wherein the bacteriophage encodes a gene product of interest either under the control of an eukaryotic promoter or as part of a fusion with a capsid protein. Claim 17 covers a method of inhibiting tumor growth or reducing tumor volume comprising administering a tumor-targeting bacterium expressing the F' pilus and a bacteriophage wherein the bacteriophage encodes a gene product of interest either under the control of a n eukaryotic promoter or as part of a fusion with a capsid protein. The bacterium may be any Gram-negative bacterium, the

gene product of interest can be virtually anything, the composition can be administered by any route, and the method can be used for treatment of any tumor-based disease.

The nature of the invention is a pharmaceutical composition comprising an attenuated, tumor-targeting Gram-negative bacterium containing a bacteriophage wherein the bacteriophage encodes a gene product of interest either under the control of an eukaryotic promoter or as part of a fusion with a capsid protein, kits comprising the pharmaceutical composition, and methods for delivering an agent and methods of inhibiting tumor growth or reducing tumor volume, wherein the methods comprise administering either a composition comprising a tumor-targeted bacterium containing a recombinant bacteriophage, or a composition comprising a tumor-targeted bacterium expressing the F' pilus and a recombinant bacteriophage encoding a gene of interest. The only disclosed use for the pharmaceutical composition is gene therapy treatment ad the claims have been examined in light of this. The delivery of a nucleic acid in vivo or ex vivo for therapeutic purposes constitutes gene therapy. Thus, the claimed methods represent methods for gene therapy.

An analysis of the prior art as of the effective filing date of the present application shows a complete lack of documented success for gene therapy. In a review on the current status of gene therapy, Mitchell ((1998) Lancet 351:346) quotes Inder Verma, a leading authority on gene therapy: "No form of gene therapy can yet be considered a success, and the major problem still lies in delivery mechanisms". Bacteria as a delivery mechanism are described as "exotic non-viral vectors". Additionally, "little is known as yet about whether these approaches will work and at the moment non-viral

vectors are too inefficient to treat genetic and most acquired diseases" (attributed to Verma). Although there is promise for progress in gene therapy, it still remains the case that "all gene-transfer methods tend to be more efficient in vitro than in vivo...so many tumour cells in the body may be left unmodified and resistant to [gene-directed enzyme prodrug therapy]" (Bonn (1999) Lancet 354:1364).

The relative skill of those in the art of recombinant DNA techniques and microbiology is high.

The area of the invention is unpredictable. As discussed above, the method of gene therapy is highly complex and unpredictable and the skilled artisan at the time of the present invention was made recognized the difficulty of achieving sufficient heterologous gene expression to induce any therapeutic effect. Thus, the effectiveness of a potential new delivery system, such as tumor-targeted bacteria containing a bacteriophage encoding a gene of interest, cannot be predicted in the absence of in vivo testing for a therapeutic effect.

The present specification provides little direction or guidance to support the claimed invention. The specification generally discloses a wide variety of possible genes of interest to be encoded by the bacteriophage, multiple routes of administration are taught, and numerous solid tumor cancers are suggested targets of the therapy. No direction is provided on how to generate tumor target bacterium in Gram-negative species other than Salmonella; indeed the basis for the tumor targeting in the Salmonella used is not disclosed thus it is unclear if one could readily generate such tumor targeting in other Salmonella strains or serotypes, unless it is an inherent

property of all Salmonella. Furthermore, no direction as to how to overcome the obstacles to gene therapy recognized by leaders in the field, i.e. the inefficiency of non-viral vectors, especially the inefficiency in in vivo usage, is provided.

No working examples are disclosed in which the method of inhibiting tumor growth or reducing tumor volume using a composition comprising a tumor-targeted bacteria is used to treat a solid tumor cancer and tumor growth is inhibited or tumor volume is reduced. An example is disclosed wherein Salmonella expressing F'pilus are infected with a phagemid in which the gene of interest is green fluorescent protein (GFP) and are used to infect mammalian M2 cells. Expression of GFP is shown. Another example discloses injecting mice containing melanoma tumors with Salmonella that are expressing F' pilus and are infected with filamentous phage M13KO7. Tumor and liver homogenates and supernatants are compared for the presence of bacteria and the presence of phage. No demonstration of gene expression or therapeutic effect due to expression of a gene of interest is made in this example. Furthermore, it is highly questionable whether a mouse model provides a basis for predictability of results in higher order mammals, specifically humans. See Gura (1997).

The quantity of experimentation necessary to carry out the claimed invention is high since the skilled artisan could not rely on the prior art of the present specification to teach how to use the claimed method. In order to demonstrate how to use the method to inhibit tumor growth or reduce tumor volume of any solid tumor cancer, on of skill in the art would have to determine if a gene of interest encoded by a bacteriophage and delivered by a bacteria is delivered efficiently and preferentially to the targeted tumor

type, if the gene of interest is expressed efficiently, and if such expression provides any therapeutic effect. Furthermore, given the broad range of possible methods of administration, one must determine if the bacterial composition would survive and bacteria would reach the targeted tumors efficiently and in sufficient number to achieve a therapeutic effect, rather than being targeted by the immune system to some degree, despite their attenuated pathogenicity. Since neither the prior art no the specification provides the answers to all of these questions it would require a large quantity of trial and error experimentation by the skilled artisan to answer these questions.

Based on the broad scope of the claims, the unpredictability in the area of the invention, the lack of sufficient guidance or working examples in the specification and the quantity of experimentation necessary, it would clearly require undue experimentation by one of skill in the art to determine how to use the claimed method comprising administering either a composition comprising a tumor-targeted bacterium containing a recombinant bacteriophage, or a composition comprising a tumor targeted bacterium expressing the F' pilus and a recombinant bacteriophage encoding a gene of interest to inhibit tumor growth or reduce tumor volume.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "the gene of interest" lacks proper antecedent basis and is thus vague and indefinite. The phrase "encode the gene of interest as a fusion protein" is vague and indefinite since a fusion protein cannot encode a gene of interest.

Markush group language must be perfected in claims 6 and 22. It would be remedial to amend the claims to read "the group consisting of".

In claim 7, it is unclear whether the limitation is intended to change the Markush group to be: "a cytokine, a bacteriocin, a pro-drug converting enzyme and an anti-angiogenic agent" or if the limitation is a composition in which the molecule is a cytotoxin which is specifically a bacteriocin. Thus, the metes and bounds of the claim cannot be determined.

In claims 11-14 and 20-23, it is unclear if "a gene product of interest" and "a gene of interest" are referring to the same thing. If they are not referring to the same thing, the meaning of "a gene of interest" is unclear as the specification only provides teachings about "a gene product of interest". Furthermore, the definition of "agent" is unclear and what this term encompasses is not expressly defined in the specification. Therefore, the claims are vague and indefinite.

Method claims 11-23 are vague and indefinite in that they lack a step which clearly relates back to the preamble. Therefore the claims are vague and indefinite.

The term "the solid tumors" in claim 19 does not have proper antecedent basis.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 24 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pawelek et al. (WO 96/40238; "Pawelek et al. (1996)") in view of Larocca et al. (US Pat. No. 6,054,312) and Sambrook et al ((1989) Molecular Cloning A Laboratory Manual Second Edition).

Pawelek et al (1996) discloses an attenuated, tumor-targeting Gram-negative bacterium which is Salmonella (p. 14, lines 1-16, 24-32) containing a plasmid modified to encode for a gene product of interest under the control of an eukaryotic promoter (p. 82, lines 23-34).

Pawelek et al (1996) does not expressly disclose an attenuated, tumor-targeting Salmonella expressing the F' pilus.

Larocca et al. discloses a bacteriophage encoding a gene of interest in a fusion with a bacteriophage capsid protein (col. 9, lines 46-49). The recombinant bacteriophage may be in the form of a phagemid (col. 4, lines 22-25). The bacteriophage are propagated in bacterial strains that carry F' episomes (col. 25, lines 46-48).

At the time the invention was made, it would have been obvious to a person of ordinary skill in the art to combine the attenuated, tumor-targeting Salmonella which delivers a gene of interest with the recombinant bacteriophage (or phagemid) encoding a gene of interest and to utilize a Salmonella strain expressing an F' pilus in the combination.

One of ordinary skill in the art would have been motivated to do this because both disclosures are directed to methods of delivering therapeutics to targeted cells See Larocca et al. Abstract and col. 10, lines 1-5, and Pawelek et al p.13, lines 20-26. In addition, both disclose treatment of solid tumor cancers including sarcomas, breast cancer, prostate cancer, melanomas, lung cancer, cervical cancer, ovarian cancer and uterine cancer. See Larocca et al col. 32, lines 41-53, and Pawelek et al p. 13, lines 26-36. Furthermore, Larocca et al. explicitly states that their recombinant bacteriophage/phagemid may be administered in a "freeze-dried" bacterium which are clearly not dead as it is further stated such bacteria "have the capacity of propagate in the intestine and release the phage". Col. 34, liens 53-56. As is well known to one of

ordinary skill in the art, a phagemid is an obvious variant of a plasmid, distinguished primarily by the presence of a filamentous phage origin of replication (Sambrook et al, pp. 4.17-4.20). It is well known that Salmonella, closely related to E. coli, may express the F' pilus and methods of accomplishing this are well known (i.e. transfect Salmonella with F plasmid using standard molecular biology techniques or mate an F' strain with the Salmonella and select for the appropriate transformants). The benefit of a Salmonella strain expressing the F' pilus is that such strains may then be infected readily by bacteriophage which serves to amplify the bacteriophage population (Sambrook et al p. 4.12), and thus also provides more efficient transduction of DNA than electroporation or other means of transformation.

Based in the entirety of the combined teachings and absent any evidence to the contrary, there would have been a reasonable expectation of success in making the invention of the combined teachings above to an attenuated, tumor-targeting Salmonella expressing the F' pilus.

Claim 24 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pawelek et al. (1997 Cancer Res. 57:4537-4544 "Pawelek et al (1997)") in view of Larocca et al. and Sambrook.

Pawelek et al (1997) discloses an attenuated, tumor-targeting Gram-negative bacterium (p. 4537, Abstract and p. 4540, second column) containing a plasmid modified to encode for a gene product of interest. The Gram-negative is Salmonella (see p. 4540), second column).

Pawelek et al (1997) does not expressly disclose an attenuated, tumor-targeting Salmonella expressing the F' pilus.

Larocca et al. discloses a bacteriophage encoding a gene of interest in a fusion with a bacteriophage capsid protein (col. 9, lines 46-49). The recombinant bacteriophage may be in the form of a phagemid (col. 4, lines 22-25). The bacteriophage are propagated in bacterial strains that carry F' episomes (col. 25, lines 46-48).

At the time the invention was made, it would have been obvious to a person of ordinary skill in the art to combine the attenuated, tumor-targeting Salmonella which delivers a gene of interest with the recombinant bacteriophage (or phagemid) and to utilize a Salmonella strain expressing an F' pilus in the combination.

One of ordinary skill in the art would have been motivated to do this because both disclosures are directed to methods of delivering therapeutics to targeted cells. See Larocca et al. Abstract and col. 10, lines 1-5, and Pawelek et al (1997) p. 4537, Abstract and p. 4542, first column. In addition, both disclose treatment of solid tumor cancers including melanoma. See Larocca et al col. 32, lines 41-53, and Pawelek et al (1997) p. 4541, first column. Furthermore, Larocca et al. explicitly states that their recombinant bacteriophage/phagemid may be administered in a "freeze-dried" bacterium which are clearly not dead as it is further stated such bacteria "have the capacity of propagate in the intestine and release the phage". Col. 34, liens 53-56. As is well known to one of ordinary skill in the art, a phagemid is an obvious variant of a plasmid, distinguished primarily by the presence of a filamentous phage origin of

replication (Sambrook et al, pp. 4.17-4.20). It is well known that Salmonella, closely related to E. coli, may express the F' pilus and methods of accomplishing this are well known (i.e. transfect Salmonella with F plasmid using standard molecular biology techniques or mate an F' strain with the Salmonella and select for the appropriate transformants). The benefit of a Salmonella strain expressing the F' pilus is that such strains may then be infected readily by bacteriophage which serves to amplify the bacteriophage population (Sambrook et al p. 4.12), and thus also provides more efficient transduction of DNA than electroporation or other means of transformation.

Based in the entirety of the combined teachings and absent any evidence to the contrary, there would have been a reasonable expectation of success in making the invention of the combined teachings above to obtain an attenuated, tumor-targeting Salmonella expressing the F' pilus.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nancy Vogel whose telephone number is (703) 308-4548. The examiner can normally be reached on 7:30 - 4:00, Monday - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, Ph.D. can be reached on (703) 305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

ntv
9/26/03

TERRY MCKELVEY
PRIMARY EXAMINER